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Host-jumping, demographic stochasticity and extinction: lytic viruses

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ABSTRACT

Question: We envision a lytic virus invading a novel-host population, when rarity of productive infections suggests a role for demographic stochasticity. We ask how functionally constrained viral trait combinations that reduce the chance of extinction (promoting invasion) might differ from traits increasing the expected growth rate of the viral population.

Mathematical methods: To focus on random variation in viral reproduction (burst size), we develop a branching process and derive the probability generating function for the number of new infections per infection. The generating function permits comparison of the extinction probability and mean growth rate for any viral life history. Then we turn to random variation in viral generation length, which sums time spent as a free virion with time reproducing within a host. We simulate this process to compare extinction frequency and mean growth rate for different combinations of viral traits.

Key assumptions: We assume infections are rare as invasion of the novel host begins, and neglect density dependence. We emphasize pleiotropic constraints, functional dependencies between viral traits governing quantity and quality of viral reproduction, and survival of free virions.

Conclusions: When pleiotropic interaction affects the burst-size distribution, with generation time fixed, extinction-resistant phenotypes increase offspring quantity, at the expense of either increased error during replication or reduced survival outside of a host, compared with growth-rate maximizing phenotypes. When pleiotropic interaction affects the random waiting time until lysis, extinction-resistant phenotypes delay lysis to gain either increased survival outside of hosts or larger bursts, at the expense of slower reproduction within hosts, compared with growth-rate maximizing phenotypes.

Keywords: burst-size variance, host-range expansion, lysis-time variation, viral extinction.

INTRODUCTION

Variation in reproductive success among generations, due to environmental stochasticity, can impact life-history evolution in large populations (Schaffer, 1974; Orzack, 1993). But random

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variation in reproductive success within a generation, due to demographic stochasticity, can govern the difference between extinction and persistence of small populations (Gillespie, 1974; Haccou and Iwasa, 1996; Fox and Kendall, 2002). Extinction probabilities, in turn, may selectively pressure life-history traits of individuals in small populations (Eshel, 1981; Fox, 1993; Shpak and Proulx, 2007). We model bacteriophage invading a novel-host population from this perspective, and analyse how stochasticity in the number of infections per infection affects phage extinction. Life-history traits are often functionally constrained (Turner and Elena, 2000; Heineman and Brown, 2012; Handel *et al.*, 2014), and so we show how antagonistic pleiotropy can discriminate extinction-resistant trait combinations from those maximizing expected growth rate.

Bacteriophage, commonly used in experimental biology (Bohannan and Lenski, 2000), may be the most abundant organisms (Abedon, 2008; Weitz and Dushoff, 2008). But the artificially high phage densities of the laboratory do not address invasion of natural host populations (Farrah, 1987; Heineman *et al.*, 2005; Buckling *et al.*, 2009), and local extinction of phage populations may occur commonly in nature (Campbell, 1961; Dennehy *et al.*, 2007; Smith and Trevino, 2009). In particular, host-range expansion may be limited by production of only a small number of free virions per infection when the virus first invades a novel host (Crill *et al.*, 2000; Kannoly, 2015); even under laboratory conditions, a few bacteriophage have a mean burst size less than 10 (Moebus, 1987; Wang, 2006).

We explore plausible assumptions about a lytic virus' invasion of a novel host and traits that reduce extinction probability (Slobodkin and Rapoport, 1974; Handel and Bennett, 2008). After we summarize the phage life cycle, we introduce a time-homogeneous branching process modelling phage growth. We derive the probability generating function for the number of infections per infection. With the generating function we calculate both the probability of ultimate extinction and expected growth for a given trait combination. Then we ask how functional trade-offs affect extinction versus mean growth. Following our analytical treatment, we present results of simulations where both burst size and lysis time vary randomly, and phage traits interact. We find that extinction-resistant viral phenotypes can differ substantially from those maximizing expected growth under reasonable hypotheses concerning pleiotropic traits, but find no difference in the absence of pleiotropy.

The infection cycle

Initially, a free virion attaches to a receptor on the surface of a host cell. Infection of the host bacterium follows, initiating the eclipse period. During eclipse, the phage genome is ejected from the virion into the host cell, and sequesters the host's biosynthetic capacity (García and Molineux, 1995). Maturation begins at the end of the eclipse period. Viral replication occurs during maturation; virions accumulate within the host-cell volume. Lysis occurs at the conclusion of maturation. Lysis ruptures the host cell's outer membrane, releasing free virions. Burst size is the number of virions released.

Some free virions decay physically in the extracellular environment (De Paepe and Taddei, 2006; Heineman and Brown, 2012). Others adsorb to either cellular debris or previously infected hosts (Aviram and Rabinovitch, 2008; Keen, 2014). To contribute to the next generation of infections, a virion must encounter a susceptible host, infect, replicate within the host, and then induce lysis. Any of these processes may impede a phage 'jumping' to a novel host, but ultimately the distribution of infections per infection will govern the probabilities of successful versus failed invasion (Crill *et al.*, 2000; Dennehy *et al.*, 2006).

RANDOM BURST SIZE

In this section, we let burst size vary randomly among infected hosts. Nutrient-driven metabolic rates differ among host cells, and phage replication varies in response to host physiology (Abedon *et al.*, 2001; Bull *et al.*, 2004); intracellular processes are intrinsically noisy. We take successive generations of infected hosts as a branching process; Table 1 lists model symbols. The virus persists as long as the number of infected hosts remains positive; zero infections is a trapping state, implying that neither infected hosts nor free virions remain. Let X_n represent the number of n^{th} generation infected hosts ($n = 0, 1, 2, \ldots$). X_0 is the number of novel-host cells initially infected; virions released from the 0^{th} generation produce the X_1 infections of the first generation. The assumption of discrete generations is tolerable; if the time scale of adsorption is fast relative to lysis time, discrete generations model lytic viruses reasonably (Patwa and Wahl, 2008).

Each of the X_n infections independently releases a random number β of free virions at lysis. Let $\Pr[\beta = b] = p_b$, where $b = 0, 1, 2, \ldots$, and $\Sigma_{b=0}^{\infty} p_b = 1$. The burst-size mean and variance, both finite, are $\mathrm{E}[\beta]$ and $\mathrm{V}[\beta]$ respectively. The probability generating function for the burst-size distribution is $G_\beta(z) = \Sigma_{b=0}^{\infty} p_b z^b$, where $|z| < 1$ (Karlin, 1966).

During the free-living stage, each virion independently infects a susceptible host at constant probabilistic rate αH. We let H represent host-cell density, a constant since infections are rare at invasion, and α is the adsorption rate. Not all virions infect host cells. Some diffuse out of the system, some attach to cellular debris, and some virions decay (Moebus, 1987; Gallet *et al.*, 2009). In the experimental absence of host cells, phage densities can decay between three and five orders of magnitude within 2 days (Lindberg, 2013), although many viruses decay more slowly (De Paepe and Taddei, 2006). Furthermore, multiple phage may attach to the same host (Smith and Trevino, 2009), but co-infection, should it occur, apparently does not affect mean burst size (Abedon, 1994). Each free-living virion independently is lost to one of these events at combined probabilistic rate ξ. Each virion released from the n^{th} generation of infections either contributes to the $(n+1)^{\text{st}}$ generation or is lost. Then the probability that a free virion infects a susceptible host, adding to the next generation of infections, is $\theta = \alpha H/(\alpha H + \xi)$. A given infection fails to generate new infections if viral reproduction fails, or if each virion released at lysis fails to infect a susceptible host cell.

Infections per infection

$F(z)$ designates the probability generating function for the number of infections in generation $(n+1)$ per infection in the n^{th} generation. Consider the i^{th} infection among the X_n independent infections of generation n. Lysis of the i^{th} infected host releases a random number of free virions β_i; let $\beta_i = b$. The number of next-generation infections arising from this single infection has a binomial distribution with expectation θb, so that the conditional generating function for the number of new infections is $F(z \mid \beta_i = b) = (1 - \theta + \theta z)^b$. Then the unconditional generating function for the number of infections per infection is $F(z) = \Sigma_{b=0}^{\infty} p_b F(z \mid \beta_i = b) = \Sigma_{b=0}^{\infty} p_b (1 - \theta + \theta z)^b$, where $(1 - \theta + \theta z) < 1$. Recalling the definition of $G_\beta(z)$, we have:

$$F(z) = G_\beta(1 - \theta + \theta z) = G_\beta\left(\frac{\alpha H z + \xi}{\alpha H + \xi}\right), \tag{1}$$

the generating function of the burst-size distribution evaluated at $(1 - \theta + \theta z)$.

Table 1. Symbols and definitions: branching process

X_n	Number of n^{th} generation infected host cells
β	Burst size, a discrete random variable
p_b	Probability $\beta = b$; $b = 0, 1, 2 \ldots$
α	Virion adsorption parameter
H	Host cell density
ξ	Free-virion loss parameter
R_0	Infections per infection when virus invades susceptible host population
σ^2	Variance in number of infections per infection
π_0	Probability of viral extinction
ρ_0	Probability any particular infection produces no new infections
ϕ	Virion-assembly error frequency, a negative binomial parameter
v	Virion maturation rate, a negative binomial parameter
v^*	Maturation rate maximizing R_0
$\tilde{v}$	Maturation rate minimizing π_0

$F(z)$ permits calculation of several quantities essential to our analysis. First, the expected number of infections per infection is $R_0 = (\mathrm{d}F/\mathrm{d}z)_{z=1} = [\alpha H/(\alpha H + \xi)]\,\mathrm{E}[\beta]$.

Second, we let σ^2 represent the variance of the number of new infections per infection. Standard methods, involving derivatives of $F(z)$ (Feller, 1957; Fox, 1993), yield, after rearrangement:

$$\sigma^2 = \frac{\alpha H \xi}{(\alpha H + \xi)^2}\,\mathrm{E}[\beta] + \left(\frac{\alpha H}{\alpha H + \xi}\right)^2 \mathrm{V}[\beta]. \tag{2}$$

Note that variance in the number of infections per infection increases with both burst-size variance and with variance in the adsorption success of free-living virions. R_0 and σ^2 are the mean and variance for a single infection; the Appendix (evolutionary-ecology.com/data/2953Appendix.pdf) lists corresponding population-level properties.

The probability that a *single infection* produces no infections is simply $F(z = 0)$. Let ρ_0 represent this probability. $\rho_0 \geq p_0$, since $\rho_0 = \Sigma_{b=0}^{\infty} p_b\,(1 - \theta)^b$.

For our analysis, the most important quantity is the extinction probability π_0. Consider the probability that the viral population goes extinct (the branching process terminates) at or before the n^{th} generation. As n increases, π_0, formally, is the limiting probability of extinction after finitely many generations (Feller, 1957). Let $X_0 = 1$; we generalize below. Assume that $R_0 > 1$; otherwise extinction is certain. Then the extinction probability π_0 satisfies (Karlin, 1966):

$$\pi_0 = F(z = \pi_0) = G_\beta(1 - \theta + \theta\pi_0). \tag{3}$$

π_0 is the smallest positive root of equation (3); $0 < \pi_0 < 1$, since $R_0 > 1$. Feller (1957) termed π_0 the chance of rapid extinction. Demographic stochasticity implies that extinction will more likely occur soon after invasion, or following disturbance reducing the number of infections to rarity (Alexander and Wahl, 2008; Allen and van den Driessche, 2013). If $X_0 > 1$, then the probability of ultimate extinction is $(\pi_0)^{X_0}$, since the various lineages are independent replicates of the same process. Then $1 - (\pi_0)^{X_0}$ is the probability that the virus successfully invades the novel host.

GROWTH RATE vs. PERSISTENCE

Dennehy and Wang (2011) found that variability in the duration of lysis increased with its mean among genotypes of a single phage. Wang (2006) reported a positive correlation between lysis time and burst size. We can infer that burst-size variance should increase with E[β]. Therefore, in this section we assume that burst-size counts follow a negative binomial probability function with parameters ν and ϕ; $\nu > 0$ and $0 < \phi < 1$ (see 2953Appendix.pdf). The mean is $\mathrm{E}[\beta] = \nu\,(1-\phi)/\phi$, and the burst-size variance is $\mathrm{V}[\beta] = \nu(1-\phi)/\phi^2 = \mathrm{E}[\beta]/\phi$. We associate ν with the pace of viral replication during the maturation period. As ν increases, the mean burst size increases and the distribution shifts from positively skewed to nearly symmetric about a single mode. We take $(1-\phi)$ as the probability that any given virion assembles properly: the likelihood that the viral genome, protein capsid, and adsorption structures are replicated and combined structurally with sufficient accuracy to infect a host cell. In some RNA viruses, the percentage of assembled virions capable of infecting the next host cell is as low as 10% (Hirst and Pons, 1973).

Given a negative binomial, the generating function for burst size is $G_\beta(z) = \phi^\nu/(1 - z + \phi z)^\nu$. Then the generating function for the count of infections per infection becomes:

$$F(z) = G_\beta(1-\theta+\theta z) = \phi^\nu \left(\phi + \frac{\alpha H}{\alpha H + \xi}\,[1-\phi]\,[1-z]\right)^{-\nu}. \tag{4}$$

The expected growth rate is $R_0 = \nu\alpha H(1-\phi)/[\phi\,(\alpha H + \xi)]$. The requirement $R_0 > 1$ implies that $\mathrm{E}[\beta] > \theta^{-1} > 1$, so that $\pi_0 < 1$. The variance in the number of infections per infection is:

$$\sigma^2 = \nu\alpha H\,(1-\phi)(\alpha H + \phi\xi)/(\phi^2[\alpha H + \xi]^2) = R_0(\alpha H + \phi\xi)/\phi(\alpha H + \xi). \tag{5}$$

Clearly, $\sigma^2/R_0 > 1$.

The probability of ultimate extinction π_0 is given by equation (4) evaluated at $z = \pi_0$ when $R_0 > 1$ and $X_0 = 1$. We can write the probability that any particular infection produces no new infections, ρ_0, directly from equation (4):

$$\rho_0 = (\phi\,[\alpha H + \xi]/[\alpha H + \phi\xi])^\nu = (R_0/\sigma^2)^\nu. \tag{6}$$

Independent traits

If viral traits are unencumbered by functional dependence, the basic reproduction number R_0, the mean growth rate of the branching process, increases as either virion maturation ν or the free-virion adsorption rate α increases. Just as clearly, R_0 decreases as either the assembly-error frequency ϕ or the free-virion loss rate ξ increases. Without trait dependence, any increase in R_0 implies a decrease in the extinction probability π_0. In the special case where $\nu = 1$, β has a geometric distribution, and $\pi_0 = R_0^{-1} < 1$. This is Whittle's (1955) approximation (Allen and van den Driessche, 2013; Lahodny *et al.*, 2014). Examination of equation (4) shows that an increase in either ϕ or ξ must increase the extinction probability π_0. Furthermore, as either α or ν increases, π_0 must decline (Fig. 1). For functionally independent traits, greater expected growth always reduces the chance of extinction.

Under antagonistic pleiotropy, improving one viral trait imposes a cost on another (Cooper and Lenski, 2000; Duffy *et al.*, 2006; Handel and Bennett, 2008). Trade-offs clearly affect life-history traits of coliform phage (De Paepe and Taddei, 2006). Genes overlap in many phage genomes, so that a single mutation can affect more than one gene product (Atkins *et al.*, 1979; Elena *et al.*, 2009;

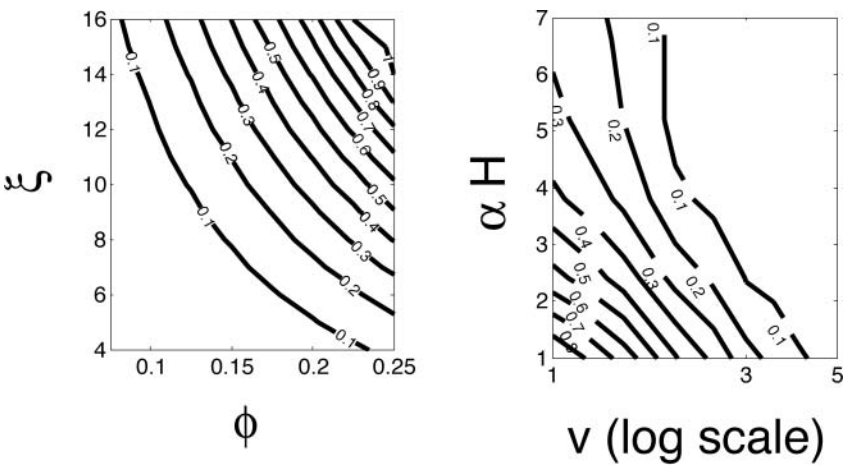

Fig. 1. Ultimate extinction probability when burst size follows the negative binomial. Left: π_0 increases strictly monotonically as either ϕ or ξ increases independently. $v = 5$, $\alpha H = 5$. Right: π_0 decreases strictly monotonically as either v or αH increases independently. $\phi = 0.1$, $\xi = 10$.

Kazaks *et al.*, 2011). Phage traits are often mediated structurally; consequently, capsid mass can play a role in trade-offs between survival and reproduction (Caraco and Wang, 2008; Dessau *et al.*, 2012).

Varying functionally dependent traits in our model can disentangle R_0 and the extinction probability π_0; the phenotype maximizing R_0 at invasion can differ, sometimes strongly, from the type minimizing the chance of extinction. A number of models find that a sufficiently large variance in reproductive success increases the chance of extinction despite a large mean (Gillespie, 1974; Moreno *et al.*, 2003; Shpak and Proulx, 2007; Lahodny *et al.*, 2014). Our model's contribution lies in recognizing how particular trade-offs can generate dependence of extinction (hence, the chance of host-jumping) on variance in reproductive success.

Faster developing, faster decaying virions

De Paepe and Taddei (2006) find that free-virion decay rate correlates strongly and positively with the rate of virion assembly within host cells. That is, $\partial\xi/\partial v > 0$ in our model. Phage with less capsid mass assemble faster. Reducing the mass of the capsid results in virions less able to withstand abiotic stress in the extracellular environment, and these virions decay faster. This trade-off links within-host replication with between-host infection transmission (Handel and Bennett, 2008; Heineman and Brown, 2012); $\partial\xi/\partial v > 0$ implies that increased intracellular reproduction reduces extracellular survival (Goldhill and Turner, 2014).

Hypothesizing a maturation–decay trade-off, we let $\xi(v) = c_1 v^{z_1}$, where $c_1, z_1 > 0$. If $z_1 \leq 1$ (so that ξ is a concave function of v), R_0 always increases with an increase in v. That is, if free-virion decay increases sufficiently slowly with maturation rate, faster virion maturation always increases R_0. But suppose $z_1 > 1$ (so that ξ is a convex function of v); then R_0 has a maximum at $v^* = (\alpha H/[c_1 (z_1 - 1)])^{1/z_1}$. If the decay rate increases sufficiently quickly with maturation rate ($z_1 > 1$), R_0 declines when $v > v^*$.

Figure 2 summarizes patterns generated when increased maturation implies greater virion decay. Each panel shows effects of increasing z_1, incrementing the pleiotropic cost of a greater maturation rate. For $z_1 = 1$, R_0 strictly increases, and π_0 strictly decreases, as

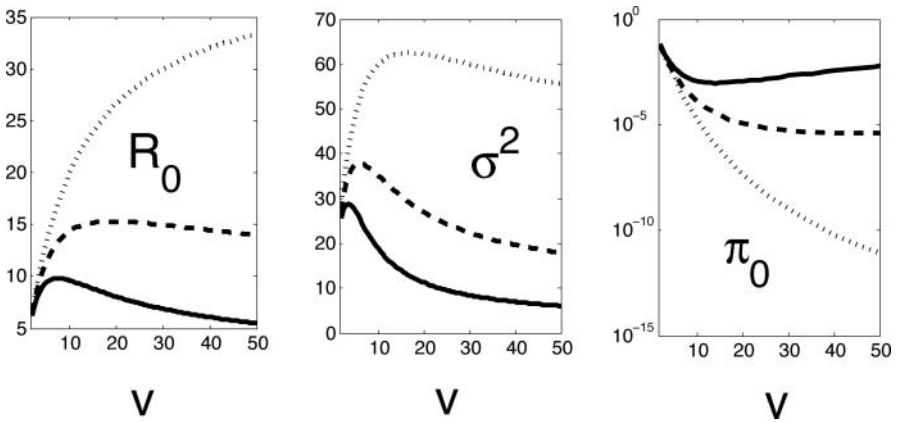

Fig. 2. Virion persistence declines as maturation rate increases: $\partial\xi/\partial v > 0$. Left: R_0; centre: σ^2 (variance in infections/infection); right: π_0, the extinction probability (semi-log scaling). Each panel: dotted line is $z_1 = 1$; dashed line is $z_1 = 1.25$; solid line is $z_1 = 1.5$. For $z_1 = 1$, π_0 always declines, and R_0 always increases, as v increases. For $z_1 = 1.25$, R_0 attains a maximum at v^*, but π_0 declines across reasonable expected burst sizes, $E[\beta] \leq 1000$. For $z_1 = 1.5$, R_0 is maximal at v^*, and π_0 is minimal at $\tilde{v} > v^*$. $\alpha H = 5$, $\phi = 0.2$; $c_1 = 0.5$.

maturation rate v increases. But when the cost function $\xi(v)$ is convex ($z_1 = 1.25$), R_0 declines sufficiently slowly past its maximum that the simultaneous decline in σ^2 combines to reduce the extinction probability further. Under sufficiently strong antagonistic pleiotropy, the extinction probability is minimal at a maturation rate beyond the value where R_0 is maximal. In our example ($z_1 = 1.5$), the phenotype maximizing R_0 has twice the extinction probability of the type minimizing the chance of extinction ($\tilde{v}$).

From Fig. 2 we see that when increasing mean burst size ($E[\beta] \sim v$) implies an accelerating increase in the probability a virion fails to produce a new infection ($1 - \theta = \xi/[\alpha H + \xi]$); R_0 is maximal when a smaller burst is combined with high virion survival. But the variance in infection counts is sufficiently large that the chance of rapid extinction continues to decline as mean burst size increases and, consequently, free-virion survival declines. Given that $R_0(v^*)$ is a maximum, π_0 may decline strictly monotonically as v increases, or $\pi_0(\tilde{v})$ will be a minimum, with $\tilde{v} > v^*$. Under strong pleiotropy, the chance of invading a novel host increases for phenotypes with a larger mean burst size, but faster decaying virions, than phenotypes maximizing mean growth. Equivalently, evading rapid extinction favours offspring quantity at the cost of offspring quality (Keen, 2014).

Less infectious, more durable virions

Durability of free-living phage requires stabilization of the receptor-binding site and (sometimes) stabilization of side-tail fibres that anchor the virion to the host's exterior. Increased structural integrity of attachment proteins will diminish virion decay rate, but also could reduce binding to host receptors (Caraco and Wang, 2008; Goldhill and Turner, 2014). In our model, this trade-off implies $\partial\xi/\partial\alpha > 0$.

Proceeding as above, we let $\xi(\alpha) = c_2\alpha^{z_2}$, where c_2, $z_2 > 0$. If $z_2 < 1$, ξ is a concave, increasing function of α, and R_0 increases strictly monotonically with α. That is, if the decay

rate increases sufficiently slowly relative to the increase in adsorption, the expected number of infections per infection must increase with the adsorption rate. But if $z_2 > 1$, R_0 decreases, strictly monotonically, as α increases. Hence, mean viral growth rate will increase (decrease) with increasing adsorption rate when the virion decay rate increases as a concave (convex) function of the adsorption parameter.

The extinction probability mirrors the simple relationship of $\xi(\alpha)$ to R_0. Using equation (1) and the hypothesized functional dependence, the extinction probability π_0 must satisfy:

$$\pi_0 = G_\beta\left(\frac{\pi_0 + [c_2/H]\,\alpha^{z_2-1}}{1 + [c_2/H]\,\alpha^{z_2-1}}\right). \tag{7}$$

Any probability generating function increases strictly in its argument. $z_2 < 1$ implies that the extinction probability declines as α increases. If $z_2 = 1$, π_0 is independent of α, whereas if $z_2 > 1$, π_0 increases with α. An increase in mean growth rate, despite any increase in the variance of infections/infection, decreases the chance of extinction, independently of the particular burst-size distribution. Figure 3 demonstrates this case for a negative binomial burst-size distribution.

Receptor specificity of adsorption often sets host-range boundaries in bacteriophage (Coetzee, 1987). Our model suggests that a trade-off between adsorption and virion decay does not imply a difference between faster growing and more extinction-resistant phenotypes during invasion of a novel host; pleiotropy affects only the 'Bernoulli trial' parameter θ. But the model does suggest that a costly trade-off ($z_2 > 1$) can render a lower adsorption rate more resistant to extinction during host invasion.

Maturation rate–assembly error trade-off

Some viral genomes are encapsulated as a set of discrete nucleic acid segments (Mindich, 1999; Sun *et al.*, 2010). Producing an infectious virion requires packaging a minimal number of

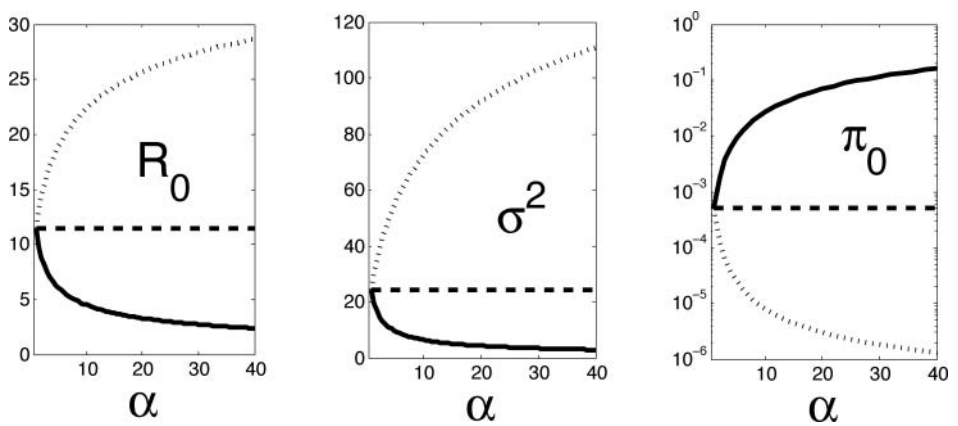

Fig. 3. Virion persistence declines as adsorption increases: $\partial\xi/\partial\alpha > 0$. Left: R_0; centre: σ^2 (variance in infections/infection); right: π_0, the extinction probability (semi-log scale). Each panel: dotted line is $z_2 = 0.5$; dashed line is $z_2 = 1$; solid line is $z_2 = 1.5$. Any increase in R_0 implies a decrease in the probability of extinction. Linear trade-off, $z_2 = 1$, renders R_0, σ^2, and π_0 independent of α. $\nu = 1$, $H = 1$, $\phi = 0.2$; $c_2 = 2.5$.

different segments to complete the genome (Odagiri and Tashiro, 1997). One model of the process, informed by the biology of influenza A virus, assumes that RNA segments are selected randomly for packaging (Hirst and Pons, 1973). Reliability of virion assembly (i.e. the proportion capable of infection) can be incremented by packaging 'extra' nucleic acid segments, increasing the likelihood that the minimal number of different segments is included (Scholtissek *et al.*, 1978; Lamb and Choppin, 1983). Hence the probability of virion assembly error declines as genome size increases.

Most double-stranded DNA bacteriophage package genetic material as a single unit (Fujisawa and Morita, 1997). They replicate the genome as a concatemer, linearly iterated copies of the full genome. A molecular motor then propels genetic material into an empty capsid; the length inserted is regulated by a 'headful' mechanism (Tétart *et al.*, 2001). A terminase cuts the DNA, and the concatemer is then available to the next virion assembled. Interestingly, the headful mechanism ensures that the terminase cuts the DNA at a length exceeding the size of a single genome (Sun *et al.*, 2010). Each virion then carries multiple copies of some gene(s). Different virions released at the same lysis carry different duplicated genes, but most virions will have a complete copy of the genome. Again, the chance of an error during virion assembly declines through an increase in the packaged genome size.

These observations indicate that larger genomes may increase functional reliability. In coliform phage, genome size correlates positively with capsid mass (and surface area) (De Paepe and Taddei, 2006), and larger virion mass reduces the assembly rate during maturation. Consequently, larger, more reliable virions develop more slowly, implying a constraint such that $\partial\phi/\partial v > 0$. Effectively, virion quality declines as burst size increases.

Hypothesizing that accelerated replication increases the chance of virion error, we let $\phi(v) = c_3 v^{z_3}$, where c_3, $z_3 > 0$, and $0 < \phi(v) < 1$. If $z_3 > 1$, $\partial R_0/\partial v < 0$. That is, if the error probability ϕ increases convexly, any increase in v reduces R_0. But if $0 < z_3 < 1$, a concave trade-off, R_0 can have a maximum at $v^* = [(1 - z_3)/c_3]^{1/z_3}$.

Figure 4 plots consequences of the maturation rate–assembly error trade-off. Each panel shows the effects of increasing the pleiotropic cost. For $0 < z_3 < 1$, R_0 attains a maximum at v^*. However, infection-number variance declines monotonically in v, and consequently the extinction probability π_0 declines monotonically as the maturation rate increases. Again, the phenotype with maximal mean growth rate does not minimize the chance of extinction.

For ($z_3 \geq 1$), the functional dependence produces a strong mean–variance interaction. As pointed out above, R_0 declines as the maturation rate increases. But σ^2 declines much more quickly. Consequently, π_0 attains a minimum at an intermediate maturation rate $\tilde{v}$.

The convex trade-off indicates that minimizing extinction offsets errors by increasing mean burst size, and extinction-resistant phenotypes can have trait combinations differing substantially from traits maximizing mean growth rate. Again, increasing offspring quantity, at the expense of offspring quality (Keen, 2014), reduces the extinction probability and so increases the chance of successful invasion of a novel host.

RANDOM LYSIS TIME

The branching process suppressed variation in the time elapsing between infections, to allow us focus on variation in infections per infection. Here, we model an infection cycle where both lysis time and adsorption time vary randomly.

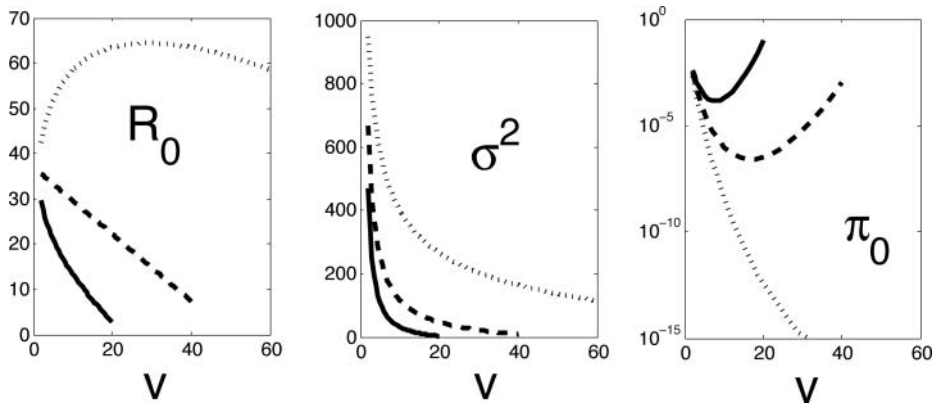

Fig. 4. Virion error increases as maturation increases: $\partial\phi/\partial v > 0$. Left: R_0; centre: σ^2 (variance in infections/infection); right: π_0, the extinction probability (semi-log scale). Each panel: dotted line is $z_3 = 0.75$, $v^* = 29$; dashed line is $z_3 = 1$; solid line is $z_3 = 1.25$. For the latter two values of z_3, extinction probability declines, despite a decrease in R_0, until $v = \tilde{v}$. $\alpha H = 5$, $\xi = 1.75$; $c_3 = 0.02$.

Time advances discretely. Each time t we count the number of free virions $P(t)$ and the number of infected host cells $I(t)$. Independently of $P(t)$ and $I(t)$, an infected cell may undergo lysis or die prior to lysis during each Δt. Otherwise, the cell remains an infected host. The probability of lysis during Δt is $\hat{v}$, the host-mortality probability is $\hat{\mu}$, and the probability of no change is $1 - \hat{v} - \hat{\mu}$ (the caret identifies simulation-model parameters; see Table 2). An infected host's longevity has mean duration $(\hat{v} + \hat{\mu})^{-1}$, and the probability that an infection leads to viral reproduction is $\hat{v}/(\hat{v} + \hat{\mu})$. Host mortality reduces $I(t)$ by one, and does not directly affect $P(t)$. When lysis occurs, $I(t)$ decreases by one, and β free virions are released.

Next, consider a free virion at time Δt. Independently of both $P(t)$ and $I(t)$, the virion may infect a host cell, may decay, or neither may occur during Δt. The probability of a new infection is $\hat{\alpha}$; infection decreases $P(t)$, and increases $I(t)$, by one. The probability the virion decays during Δt is $\hat{\xi}$; decay decreases $P(t)$ by one. The probability of no change is $1 - \hat{\alpha} - \hat{\xi}$. The expected time over which a virion remains free is $(\hat{\alpha} + \hat{\xi})^{-1}$, and the probability that a free virion ever infects a new host is $\hat{\alpha}/(\hat{\alpha} + \hat{\xi})$.

Table 2. Symbols and definitions: simulation model

$P(t)$	Free virions at time t
$I(t)$	Infected hosts at time t
$\hat{v}$	Probability of lysis
$\hat{\mu}$	Probability infected host dies; prevents lysis
$\hat{\alpha}$	Probability free virion infects host
$\hat{\xi}$	Probability free virion decays
$\beta_{\max}$	Maximal burst size
λ	Finite rate of increase when extinction averted

Since the virus is rare during invasion, we assume host density to be constant and treat it implicitly. The dynamics of the conditional expectations becomes:

$$\mathrm{E}[(P(t+\Delta t) \mid P_t, I_t)] = (1 - \hat{\alpha} - \hat{\xi})P_t + \mathrm{E}[\beta]\hat{v}I_t, \tag{8}$$

$$\mathrm{E}[(I(t+\Delta t) \mid P_t, I_t)] = \alpha P_t + (1 - \hat{v} - \hat{\mu})I_t, \tag{9}$$

for $P(t)$, $I(t) \geq 0$. The process will either exhibit rapid extinction or will grow very large if extinction is averted.

This section treats burst size β as a discrete random variable independent of lysis and adsorption times; we consider the negative binomial, discrete uniform, and a discrete normal distribution. We also take β as a constant, to isolate effects of random duration in the infection cycle. Finally, we let burst size increase with the expected duration of the lysis period (Wang, 2006). We assume that all virions released at lysis can productively infect a susceptible host.

Simulated host-jumping

We initialized the infection dynamics at $[P(0) = 0, I(0) = 1]$, a single infection and no free virions. A simulation ended when the first terminating event occurred: viral extinction $[P(t) = I(t) = 0]$, or the virus remained extant for 25 time units. For each parameter combination, we estimated π_0 by the frequency of extinction among 500 simulations. When the virus escaped extinction through $t = 25$ (i.e. conditional on persistence), we took the realized finite rate of increase as $\lambda = [I(25)/I(0)]^{1/25}$.

Note that neglecting demographic stochasticity yields a stage-structured model. The asymptotic growth rate AG is the leading eigenvalue of the matrix of stage-structured transitions:

$$AG = 1 - \tfrac{1}{2}(\hat{\alpha} + \hat{\mu} + \hat{v} + \hat{\xi}) + X, \tag{10}$$

where

$$X = \tfrac{1}{2}[([\hat{\alpha} + \hat{\xi}] - [\hat{v} + \hat{\mu}])^2 + 4\hat{\alpha}\hat{v}B]^{1/2} \tag{11}$$

and $B = \mathrm{E}[\beta]$.

We report two simulation series. The first series assumed that more persistent virions require lengthier maturation. Hence a greater lysis probability $\hat{v}$ implied an increased decay probability $\hat{\xi}$. We let $\hat{\xi}(\hat{v}) = c_4\hat{v}^2$, choosing c_4 so that $0 < \hat{\xi}(\hat{v}) + \hat{\alpha} < 1$. In simulations assuming independent traits (i.e. $\hat{\xi}$ did not depend functionally on $\hat{v}$), we found that any increase in the realized growth rate λ implies a decrease in extinction probability π_0. As in the branching process, pleiotropic interaction is required for differences between faster-growing and extinction-resistant trait combinations.

The second simulation series addressed dependence of burst size on lysis time. A longer lysis period can allow more virions to mature (Wang *et al.*, 1996; Heineman and Bull, 2007). Extending the expected duration of an infection might change the expected growth rate, but it necessarily will increase the chance that an infected host dies before lysis, resulting in failed (or inordinately delayed) viral reproduction. To implement these assumptions, we let $\beta = \beta_{\max}(1 - \hat{v})$, so that $\partial\beta/\partial\hat{v} < 0$; faster lysis limits burst size, but increases the chance of

successful reproduction ($\hat{\mu}$ is fixed). Under these simple assumptions, the expected number of infections per infection is:

$$\hat{R}_0 = \beta_{\max}\,\hat{\alpha}\hat{v}\,(1-\hat{v})/(\hat{v}+\hat{\mu})\,(\hat{\alpha}+\hat{\xi}).$$

$\hat{R}_0$ has a maximum when $\hat{v}_* = \sqrt{\hat{\mu}^2+\hat{\mu}} - \hat{\mu}$, provided that $0 < \hat{v}_* + \hat{\mu} \leq 1$. Note that $\hat{R}_0$ is an infection number, not a rate; the model's mean growth rate is given by equation (10).

Virion survival trade-off

Figure 5 shows simulation results when faster lysis accelerated the decay of free virions. These results, whether burst size was fixed or followed any of three discrete probability distributions, reveal that more extinction-resistant trait combinations have greater persistence (lower $\hat{\xi}$), hence longer lysis times, than do phenotypes maximizing average growth conditional on survival. These examples are typical for the extensive simulation series. Longer lysis time reduces model growth rate but increases the fraction of free virions that successfully infect a host; the consequence is reduced extinction frequency, compared with growth-rate maximization. In these results, the most extinction-resistant invaders have relatively low realized growth rates. Furthermore, maximizing the growth rate of the model's deterministic approximation (equation 10) implies near-certain extinction in these examples, hence almost certain failure invading the novel host.

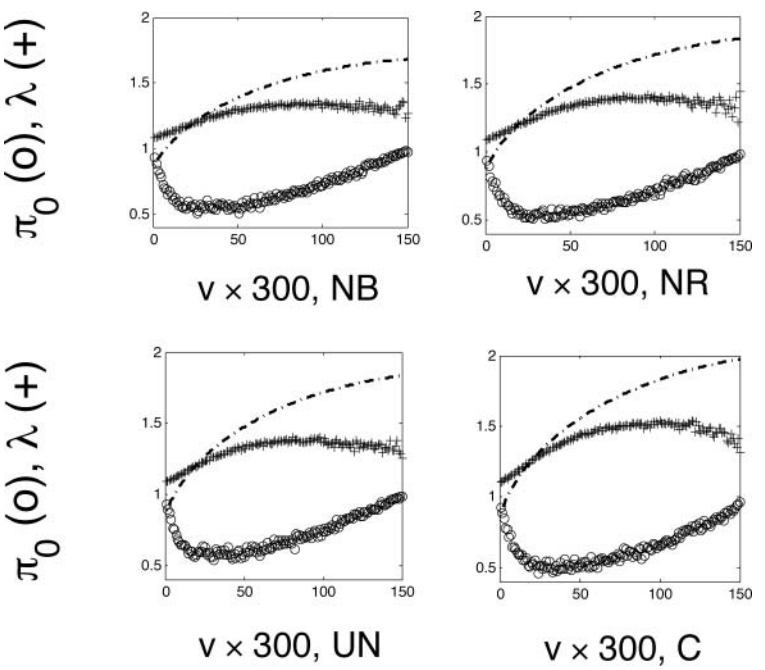

Fig. 5. Pleiotropy and virion decay probability $\hat{\xi}$. $\partial\hat{\xi}/\partial\hat{v} > 0$; $\hat{\xi}(\hat{v}) = 1.5\ \hat{v}^2$, $\hat{\alpha} = 0.65$, and $\hat{\mu} = 0.15$. Top left: burst size follows negative binomial with mean = 7, variance = 14. Top right: burst size follows discrete normal with mean = 8.5, variance = 16. Lower left: burst size follows uniform with mean = 8.5. Lower right: fixed burst size = 10. In each plot, o is $\pi_0 < 1$, + is $\lambda > 1$, and the broken line is the asymptotic growth rate, equation (10).

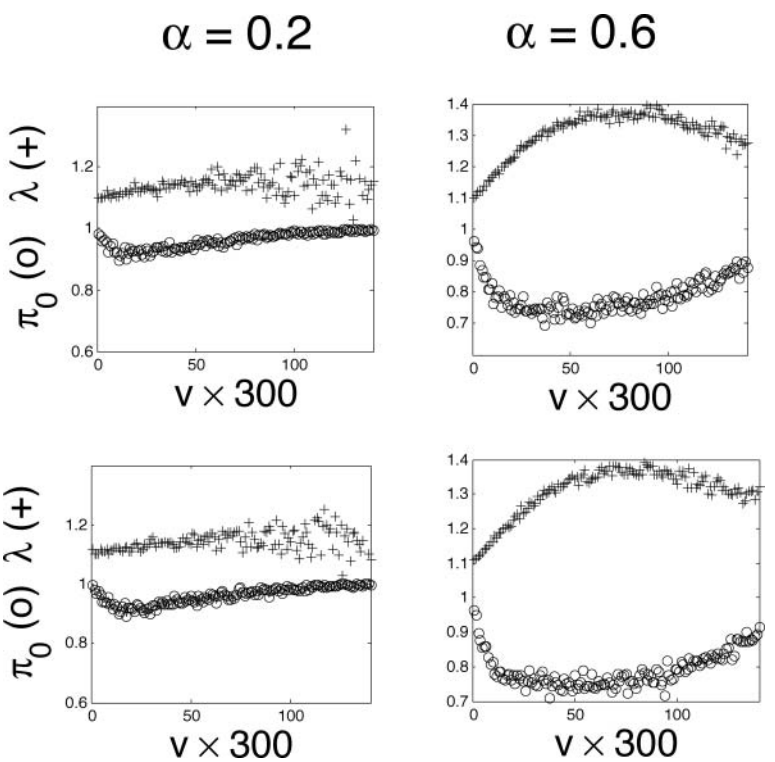

Fig. 6. Burst size increases with lysis time. $\beta = 12\ (1 - \hat{v})$. Each plot: $\hat{\xi} = 0.25$; in each plot, o is $\pi_0 < 1$, + is $\lambda > 1$. When $\hat{\alpha} < \hat{\xi}$ (left column), virion decay exceeds successful infection; when $\hat{\alpha} > \hat{\xi}$ (right column), the majority of free virions infect a host; extinction probabilities are lower, and realized growth rates are higher. Upper row, $\hat{\mu} = 0.5$; lower row, $\hat{\mu} = 0.1$.

Lysis probability and burst size

Figure 6 shows results when burst size increases with mean lysis time. Equivalently, a larger lysis probability implies a greater chance of successful reproduction, but a smaller burst. Reduced extinction probabilities are associated, although only weakly, with lower lysis probabilities, hence with longer lysis times and larger burst sizes. We did not observe the opposite result in simulation.

Summary of results

The branching process treated demographic stochasticity as random variation in the number of infections per infection. The model assumed that varying functionally dependent viral traits altered both the mean and variance of infection number. When virion decay increased with maturation rate, and when virion reliability declined with maturation rate, the biological results were similar. Compared with phenotypes with maximal expected infection number, extinction-resistant phenotypes had lower mean infection number, but also had a lower variance in the number of infections per infection. The 'mechanism' yielding extinction resistance was production of more virions of lower quality, i.e. π_0

declined as burst size grew, and as the mean and variance of infection number declined. Good invaders avoid too great a variance in infections produced, though not necessarily variance in burst size *per se* (Smallwood, 1996; Caraco, 1998; Rubenstein, 2011). However, when virion decay increased as a power function of adsorption probability, any trait variation that increased the mean infection number simultaneously decreased the extinction probability.

The first simulation series focused on demographic stochasticity in the duration of the infection cycle, hence generation length. The functional dependence linked the time elapsing between infection and lysis (via lysis probability) to the virion decay probability (which affects the probability of adsorption before decay). Compared with phenotypes with larger mean growth rates, given that they invade the novel host, extinction-resistant trait combinations produced virions with greater survival in the extra-host environment, at a cost of a longer time between infections (lower lysis probability).

Our final simulations assumed that burst size increased as lysis probability decreased, which, in turn, decreased the probability of successful reproduction. Again, extinction-resistance appears to favour slower lysis and greater burst size than found in trait combinations with larger mean growth rates.

DISCUSSION

Several recent epidemics in human populations have been preceded by viral host-range expansion (Crill *et al.*, 2000; Woolhouse *et al.*, 2005). Ordinarily, viral host-jumping begins with a period where the virus must overcome ecological challenges of niche expansion: slow adsorption to, and low reproduction within, the novel host (Dennehy *et al.*, 2006). Furthermore, host-range expansion will ordinarily begin with only a few infections, particularly if only a rare mutant can successfully infect the novel host. Therefore, we focus on extinction versus persistence when encountering a new host. Once the virus has invaded the novel host ecologically, genetic adaptation may improve its performance.

Each of our analyses makes different assumptions, to ask different questions. We see that when functional dependence involves burst size, extinction declines as burst size increases, despite a reduction in virion survival (branching process) or in the chance a host survives until lysis (second simulation set). Furthermore, we see that when functional dependence involves the length of the lysis period, extinction-resistant phenotypes, compared with types with larger growth rates, extend the expected time to lysis, to increase survival of free virions (first simulation set) or to increase reproduction given survival (second simulation set).

Our models differ from recent applications of branching processes to experimental evolution of phage (Hubbarde *et al.*, 2007; Alexander and Wahl, 2008); we emphasize that functional constraints on viral life-history traits are common and important. Rather than equating successful host-jumping with rapid proliferation, we invoke an idea in Slobodkin and Rapoport (1974). Persisting through rarity when a novel host is first infected will usually precede an increase in abundance, and our examples suggest that extinction-resistance when rare may sometimes require (or favour) traits distinct from those maximizing average growth. Pleiotropic effects between phage traits may be exaggerated during an increase in niche breadth (Duffy *et al.*, 2006). Keen (2014) hypothesizes that increased host range slows virion development, reducing burst size.

Empirical evidence clearly indicates that trade-offs do, in some cases, constrain trait combinations of lytic-virus life histories (Turner and Elena, 2000). Note, however, that pleiotropy in phage may be negative or positive (Evans *et al.*, 2010). Interestingly, McGee *et al.* (2014),

working with laboratory phage, selected for rapid growth within hosts. They found that increased growth reduced virion stability in the extracellular environment, the sort of trade-off we assume. Separately, the authors alternated selection for faster within-host growth and capsid stability in a harsh extracellular environment. Each trait improved; no trade-off was detected.

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REFERENCES

Abedon, S.T. 1994. Lysis and the interaction between free phages and infected cells. In *The Molecular Biology of Bacteriophage T4* (J.D. Karam, J.W. Drake and K. Kreuzer, eds.), pp. 397–405. Washington, DC: ASM Press.

Abedon, S.T. 2008. *Bacteriophage Ecology: Population Growth, Evolution, and Impact of Bacterial Viruses*. Cambridge: Cambridge University Press.

Abedon, S.T., Herschler, T.D. and Stopar, D. 2001. Bacterophage latent-period evolution as a response to resource availability. *Appl. Environ. Microbiol.*, **67**: 4233–4241.

Alexander, H.K. and Wahl, L.M. 2008. Fixation probabilities depend on life history: fecundity, generation time and survival in a burst-death model. *Evolution*, **62**: 1600–1609.

Allen, L.J.S. and van den Driessche, P. 2013. Relations between deterministic and stochastic models for disease extinction in continuous- and discrete-time infectious disease models. *Math. Biosci.*, **243**: 99–108.

Atkins, J.F., Steitz, J.A., Anderson, C.W. and Model, P. 1979. Binding of mammalian ribosomes to MS2 phage RNA reveals an overlapping gene encoding a lysis function. *Cell*, **18**: 247–256.

Aviram, I. and Rabinovitch, A. 2008. Dynamical types of bacteria and bacteriophages interaction: shielding by debris. *J. Theor. Biol.*, **251**: 121–136.

Bohannan, B.J.M. and Lenski, R.E. 2000. Linking genetic change to community evolution: insights from studies of bacteria and bacteriophage. *Ecol. Lett.*, **3**: 362–377.

Buckling, A., Maclean, R.C., Brockhurst, M.A. and Colegrave, N. 2009. The *Beagle* in a bottle. *Nature*, **257**: 824–829.

Bull, J.J., Pfennig, D.W. and Wang, I.-N. 2004. Genetic details, optimization and phage life histories. *Trends Ecol. Evol.*, **19**: 76–82.

Campbell, A. 1961. Conditions for existence of bacteriophages. *Evolution*, **15**: 153–165.

Caraco, T. 1998. Bet-hedging. In *Encyclopedia of Ecology and Environmental Management* (P. Calow, ed.), pp. 76–77. Oxford: Blackwell Science.

Caraco, T. and Wang, I.-N. 2008. Free-living pathogens: life-history constraints and strain competition. *J. Theor. Biol.*, **250**: 569–579.

Coetzee, J.N. 1987. Bacteriophage taxonomy. In *Phage Ecology* (S.M. Goyal, C.P. Gerba and G. Bitton, eds.), pp. 45–85. New York: Wiley.

Cooper, V.S. and Lenski, R.E. 2000. The population genetics of ecological specialization in evolving *Escherichia coli* populations. *Nature*, **407**: 736–739.

Crill, W.D., Wachman, H.A. and Bull, J.J. 2000. Evolutionary reversals during viral adaptation to alternating hosts. *Genetics*, **154**: 27–37.

Dennehy, J.J. and Wang, I.-N. 2011. Factors influencing lysis time stochasticity in bacteriophage λ. *BMC Microbiol.*, **11**: 174.

Dennehy, J.J., Friedenberg, N.A., Holt, R.D. and Turner, P.E. 2006. Viral ecology and the maintenance of novel host use. *Am. Nat.*, **167**: 429–439.

Dennehy, J.J., Friedenberg, N.A., Yang, Y.W. and Turner, P.E. 2007. Virus population extinction via ecological traps. *Ecol. Lett.*, **10**: 230–240.

De Paepe, M. and Taddei, F. 2006. Viruses' life history: towards a mechanistic basis of a trade-off between survival and reproduction among phages. *PLoS Biol.*, **4**: 1248–1256.

Dessau, M., Goldhill, D., McBride, R.L., Turner, P.E. and Modis, Y. 2012. Selective pressure causes an RNA virus to trade reproductive fitness for increased structural and thermal stability of a viral enzyme. *PLoS Genetics*, **8**: e1003102.

Duffy, S., Turner, P.E. and Burch, C.L. 2006. Pleiotropic costs of niche expansion in the RNA bacteriophage ϕ6. *Genetics*, **172**: 751–757.

Elena, S.F., Agudelo-Romero, P. and Lalie, J. 2009. The evolution of viruses in multi-host fitness landscapes. *Open Virol. J.*, **3**: 1–6.

Eshel, I. 1981. On the survival probability of a slightly advantageous mutant gene with a general distribution of progeny size – a branching process model. *J. Math. Biol.*, **12**: 355–362.

Evans, T., Bowers, R.G. and Mortimer, M. 2010. Adaptive dynamics of temperate phages. *Evol. Ecol. Res.*, **12**: 413–434.

Farrah, S.R. 1987. Ecology of phage in freshwater environments. In *Phage Ecology* (S.M. Goyal, C.P. Gerba and G. Bitton, eds.), pp. 125–136. New York: Wiley.

Feller, W. 1957. *An Introduction to Probability Theory and Its Applications I*. New York: Wiley.

Fox, G.A. 1993. Life history evolution and demographic stochasticity. *Evol. Ecol.*, **1**: 1–14.

Fox, G.A. and Kendall, B.E. 2002. Demographic stochasticity and the variance reduction effect. *Ecology*, **83**: 1928–1934.

Fujisawa, H. and Morita, M. 1997. Phage DNA packaging. *Genes to Cells*, **2**: 537–545.

Gallet, R., Shao, Y. and Wang, I.-N. 2009. High adsorption rate is detrimental to bacteriophage fitness in a biofilm-like environment. *BMC Evol. Biol.*, **9**: 241.

García, L.R. and Molineux, I.J. 1995. Rate of translocation of bacteriophage T7 DNA across membranes of *Escherichia coli*. *J. Bacteriol.*, **177**: 4066–4076.

Gillespie, J. 1974. Natural selection for within-generation variance in offspring number. I. *Genetics*, **76**: 601–606.

Goldhill, D.H. and Turner, P.E. 2014. The evolution of life history trade-offs in viruses. *Curr. Opin. Virol.*, **8**: 79–84.

Haccou, P. and Iwasa, Y. 1996. Establishment probability in fluctuating environments: a branching process model. *Theor. Pop. Biol.*, **50**: 254–280.

Handel, A. and Bennett, M.R. 2008. Surviving the bottleneck: transmission mutants and the evolution of microbial populations. *Genetics*, **180**: 2193–2200.

Handel, A., Lebarbenchon, C., Stalknecht, D. and Rohani, P. 2014. Trade-offs between and within scales: environmental persistence and within-host fitness of avian influenza viruses. *Proc. R. Soc. Lond. B*, **281**: 20133051.

Heineman, R.H. and Brown, S.P. 2012. Experimental evolution of a bacteriophage virus reveals the trajectory of adaptation across a fecundity/longevity trade-off. *PLoS One*, **7**: e46322.

Heineman, R.H. and Bull, J.J. 2007. Testing optimality with experimental evolution: lysis time in a bacteriophage. *Evolution*, **61**: 1695–1709.

Heineman, R.H., Molineux, I.J. and Bull, J.J. 2005. Evolutionary robustness of an optimal phenotype: re-evolution of lysis in a bacteriophage deleted for its lysin gene. *J. Mol. Evol.*, **61**: 181–191.

Hirst, G.K. and Pons, M.W. 1973. Mechanism of influenza recombination. II. Virus aggregation and its effect on plaque formation by so-called noninfective virus. *Virology*, **56**: 620–631.

Hubbarde, J.E., Wild, G. and Wahl, L.M. 2007. Fixation probabilities when generation times are variable: the burst-death model. *Genetics*, **176**: 1703–1712.

Kannoly, S. 2015. Characterization of ssRNA phages C-1 and Hgal1: interactions of phage Hgal1 with five Enterobacteriaceae species. Dissertation, University at Albany.

Karlin, S. 1966. *A First Course in Stochastic Processes*. New York: Academic Press.

Kazaks, A., Voronkova, T., Rumnieks, J., Dishlers, A. and Tars, K. 2011. Genome structure of Caulobacter phage phiCb5. *J. Virol.*, **85**: 4628–4631.

Keen, E.C. 2014. Tradeoffs in bacteriophage life histories. *Bacteriophage*, **4**: e28365.

Lahodny, G.E., Gautam, R. and Ivanek, R. 2014. Estimating the probability of an extinction event or major outbreak for an environmentally transmitted infectious disease. *J. Biol. Dynamics*, **9** (suppl. 1): 128–155.

Lamb, R.A. and Choppin, P.W. 1983. The gene structure and replication of influenza virus. *Annu. Rev. Biochem.*, **52**: 467–506.

Lindberg, H. 2013. Phage life history traits: regulation of *Pseudomonas aeruginosa* and evolution of phage resistance within the *Drosophila melanogaster* host environment. Dissertation: State University of New York at Albany.

McGee, L.W., Aitchison, E.W., Caudle, S.B., Morrison, A.J., Zheng, L., Yang, W. *et al.* 2014. Payoffs, not tradeoffs, in the adaptation of a virus to ostensibly conflicting selection pressures. *PLoS Genetics*, **10**: e1004611.

Mindich, L. 1999. Precise packaging of the three genomic segments of the double-stranded-RNA bacteriophage ϕ6. *Micribiol. Molec. Biol. Rev.*, **63**: 149–160.

Moebus, K. 1987. Ecology of marine bacteriophages. In *Phage Ecology* (S.M. Goyal, C.P. Gerba and G. Bitton, eds.), pp. 137–156. New York: Wiley.

Moreno, J., Polo, V., Sanz, J.J., de León, A., Minguez, E. and Weiga, J.P. 2003. The relationship between population means and variances in reproductive success: implications of life history and ecology. *Evol. Ecol. Res.*, **5**: 1223–1237.

Odagiri, T. and Tashiro, M. 1997. Segment-specific noncoding sequences of the influenza virus genome RNA are involved in the specific competition between defective interfering RNA and its progenitor RNA segment at the virion assembly step. *J. Virol.*, **71**: 2138–2145.

Orzack, S.H. 1993. Life history evolution and population dynamics in variable environments: some insights from stochastic demography. In *Lecture Notes in Biomathematics 98: Adaptation in Stochastic Environments* (J. Yoshimura and C.W. Clark, eds.), pp. 63–104. Berlin: Springer.

Patwa, Z. and Wahl, L.M. 2008. Fixation probability for lytic viruses: the attachment-lysis model. *Genetics*, **180**: 459–470.

Rubenstein, D.R. 2011. Spatiotemporal environmental variation, risk aversion, and the evolution of cooperative breeding as a bet-hedging strategy. *Proc. Natl. Acad. Sci. USA*, **108**: 10816–10822.

Schaffer, W.M. 1974. Optimal reproductive effort in fluctuating environments. *Am. Nat.*, **108**: 783–790.

Scholtissek, C., Rohde, W., Harms, E., Rott, R., Orlich, M. and Bochek, C.B. 1978. A possible partial heterozygote of an influenza A virus. *Virology*, **89**: 506–526.

Shpak, M. and Proulx, S.R. 2007. The role of life cycle and migration in selection for variance in offspring number. *Bull. Math. Biol.*, **69**: 837–860.

Slobodkin, L.B. and Rapoport, A. 1974. An optimal strategy of evolution. *Quart. Rev. Biol.*, **49**: 181–200.

Smallwood, P.D. 1996. An introduction to risk sensitivity: the use of Jensen's Inequality to clarify evolutionary arguments of adaptation and constraint. *Am. Zool.*, **36**: 392–401.

Smith, H.L. and Trevino, R.T. 2009. Bacteriophage infection dynamics: multiple host binding sites. *Math. Model. Nat. Phenom.*, **4**: 111–136.

Sun, S., Rao, V.B. and Rossman, M.G. 2010. Genome packaging in viruses. *Curr. Opin. Struct. Biol.*, **20**: 114–120.

Tétart, F., Desplats, C., Kutateladze, M., Monod, C., Ackermann, H.-W. and Krisch, H.M. 2001. Phylogeny of the major head and tail genes of the wide-ranging T4-type bacteriophages. *J. Bacteriol.*, **183**: 358–366.

Turner, P.E. and Elena, S.F. 2000. Cost of host radiation in an RNA virus. *Genetics*, **156**: 1465–1470.

Wang, I.-N. 2006. Lysis timing and bacteriophage fitness. *Genetics*, **172**: 17–26.

Wang, I.-N., Dykhuizen, D.E. and Slobodkin, L.B. 1996. The evolution of phage lysis timing. *Evol. Ecol.*, **10**: 545–558.

Weitz, J.S. and Dushoff, J. 2008. Alternative stable states in host-phage dynamics. *Theor. Ecol.*, **1**: 13–19.

Whittle, P. 1955. The outcome of a stochastic epidemic: a note on Bailey's paper. *Biometrika*, **42**: 116–122.

Woolhouse, M.E.J., Haydon, D.T. and Antia, R. 2005. Emerging pathogens: the epidemiology and evolution of species jumps. *Trends Ecol. Evol.*, **20**: 238–244.